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Dr. David G. White Named Director of CVM's Office of Research

by Jon F. Scheid, Editor

Dr. David G. White, a microbiologist with extensive experience in various academic and regulatory research settings, was named Director of the Center for Veterinary Medicine's Office of Research in December 2008.

Immediately prior to this appointment, Dr. White was Director of the Division of Animal and Food Microbiology in the Office of Research and Program Director for the Food and Drug Administration's National Antimicrobial Resistance Monitoring System.

The previous OR Director, Dr. Marleen Wekell, has become Director of the Office of Applied Research and Safety Assessment in FDA's Center for Food Safety and Applied Nutrition.

Plans for the Office of Research

Dr. White's goals for the Office include increasing coordination within CVM and FDA, particularly the Center for Food Safety and Applied Nutrition, which has its own research laboratory facilities (now run by Dr. Wekell).

The Office of Research, located in Laurel, MD, has several laboratories, as well as 165 acres of pasture land and several large animal facilities. The site also has an extensive aquaculture research facility, headed by Dr. Renate Reimschuessel, a research biologist.

Dr. White said in a recent interview with *FDA Veterinarian* that the staff and the site at the Office of Research are especially suited for research to establish animal drug residue detection methods and to research the development of antimicrobial drug resistance.

Dr. David G. White

The Office of Research supported the Center for Food Safety and Applied Nutrition during the investigation of *Salmonella*-contaminated peanuts, Dr. White said. Office researchers helped further identify the *Salmonella* found in the contaminated food by characterizing antimicrobial susceptibility patterns, which helped FDA determine the source and distribution of the contaminated products.

Dr. White said he would like to expand the Office of Research's capabilities for responding to emergencies by enhancing its ability to detect contaminants, including those intentionally added as well as accidental. Office of Research staff demonstrated their expertise in this area during the melamine-contaminated pet food crisis, he said. The Office of Research played a key role in developing melamine detection methods.

For the future, Dr. White wants to expand the Office's capabilities in the area of pharmacogenomics, which in CVM's case will focus on how genetic variation in animals influences the safety and effectiveness of drug products administered to those animals. Research in this area relating to veterinary medicine is increasing as an offshoot of "personalized" human medicine, he said. Within a few years, animal health companies most likely will be developing veterinary drugs tailored to an animal's genetic profile, he predicted. As those drugs are developed, the Office of Research's role will be to develop methods or screens for the detection of novel biomarkers associated with particular animal genetic profiles so that veterinary drug safety and effectiveness can be optimized.

Another area that the Office is gearing up for is genetic engineering, Dr. White said. Office of Research has already been involved to some extent,

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PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

FDA Continues *Salmonella* Outbreak Investigation

by Chandra Smith-Collier, Communications Staff

The outbreak of salmonellosis associated with contaminated peanut butter products has spread to pets.

In early December 2008, the Food and Drug Administration, in collaboration with the Centers for Disease Control and Prevention (CDC), the U.S. Department of Agriculture's Food and Safety and Inspection Service, and various State and local health departments, began to investigate the multi-State outbreak of illnesses in humans caused by *Salmonella* Typhimurium. In addition to humans, animals may also have been affected, according to reports.

As of the beginning of February 2009, CDC reported that 600 persons from 44 States plus one person from Canada had been infected with the outbreak strain of *Salmonella* Typhimurium and that the infection may have contributed to eight deaths.

The large number of products and brands recalled already, and the large quantities of some recalled products, makes this one of the largest food recalls ever in the United States.

In addition, a laboratory has confirmed a case of *Salmonella* in a dog

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Dr. David G. White Named... *(Continued)*

as Dr. Haile Yancy, a research biologist in the Division of Animal Research, led the development of a Polymerase Chain Reaction method to detect the recombinant DNA in the genetically engineered goats used to produce a biologic product for human use. (See "FDA Approves FIrst GE Animal, Human Health Product" on page 3.)

The product, ATryn, which was approved in February, is an anticoagulant used for the prevention of blood clots in patients who have a rare disease known as hereditary antithrombin (AT) deficiency. ATryn is a therapeutic protein derived from the milk of genetically engineered goats.

CVM assessed the safety of the rDNA construct to the genetically engineered goats. The assessment included a full review of the construct and its stability in the genome of the goats over seven generations. In the review, CVM found no adverse outcomes of the genetic engineering.

While expanding its capabilities, the Office of Research will maintain high standards, Dr. White said. His goals for the Office are to make sure it is known nationally and internationally for its quality of work. He will also try to reach out to other laboratories and scientists for collaboration, to "leverage" research work, he said.

And, he will encourage OR scientists to publish as much of their work as possible so it has the greatest value.

Dr. White's background

Along with his post as Office of Research Director, Dr. White currently serves as co-chair of the FDA Antimicrobial Resistance Steering Committee and the U.S. Interagency Task Force on Antimicrobial Resistance. He is also the U.S. Delegate to the Codex Ad Hoc Intergovernmental Task Force on Antimicrobial Resistance, which held its second meeting in 2008.

Prior to coming to FDA, Dr. White was an assistant professor in the Department of Veterinary and Microbiological Sciences at North Dakota State University.

He is a past member of the subcommittee of Veterinary Antimicrobial Susceptibility Testing, Clinical and Laboratory Standards Institute, and the ad hoc group on Antimicrobial Resistance, Office of international des Epizooties. He is a founding member of the Reservoirs of Antibiotic Resistance, which is working to expand scientific understanding of the role commensal bacteria play in spreading antimicrobial resistance.

Dr. White has also served on several extramural and intramural research panels. He is also an editor of the 2005 book, *Frontiers in Antibiotic Resistance*, published by ASM Press, Washington, D.C.

Dr. White's career focus has been on the development, dissemination, and persistence of bacterial resistance to antimicrobials used in animal production environments, and on the assessment of the implications of resistance to animal and human medicine.

Dr. White received his Bachelor's degree from the University of Vermont, Masters of Science degree from the University of Kentucky, and Ph.D. from the Pennsylvania State University. Also, he was a post-doctoral fellow at the Center for Adaptation Genetics and Drug Resistance at Tufts University School of Medicine, where he studied the characterization of the multiple antibiotic resistance locus in *Escherichia coli*.

FDA VETERINARIAN

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FDA Approves First GE Animal, Human Health Product

by Jon F. Scheid, Editor

The Food and Drug Administration announced in February that it had approved the first human health product, a biologic, made from a genetically engineered (GE) animal, and the first recombinant DNA (rDNA) construct in a GE animal.

The human health product is ATryn, an anticoagulant used for the prevention of blood clots in patients with a rare disease known as hereditary antithrombin (AT) deficiency.

ATryn is a therapeutic protein derived from the milk of GE goats. The goats have been genetically engineered by the introduction of an rDNA construct with instructions for the goats to produce human antithrombin in their milk. Antithrombin is a protein that naturally occurs in healthy individuals and helps to keep blood from clotting in the veins and arteries.

ATryn is manufactured by GTC Biotherapeutics, Inc., Framingham, MA.

FDA finalized a Guidance for Industry about GE animals just the month before. The guidance, titled "Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs," explains FDA's current thinking about how it will regulate GE animals.

FDA's regulation of GE animals will require no new rules or laws. According to the guidance, FDA is regulating the rDNA constructs in GE animals under the new animal drug provisions of the Federal Food, Drug, and Cosmetic Act. One of the definitions of a new animal drug under the Act is *"an article (other than food) intended to affect the structure or any function of the body of man or other animals…."* According to that definition, an rDNA construct intended to affect the structure or function of an animal meets the definition of a new animal drug, regardless of the intended use of the resulting GE animals.

The guidance strongly encourages sponsors to consult with FDA early in

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…*Salmonella* Outbreak Investigation *(Continued)*

from an Oregon household. Further characterization of this *Salmonella* isolate was pending as of late February, but *Salmonella* resembling the outbreak strain was isolated by a private laboratory from recalled peanut butter flavored dog biscuits from this dog's household. At least three States have reported incidents of dogs that have shown gastrointestinal signs consistent with *Salmonella* infection, and those animals are known to have consumed peanut butter products mentioned on the FDA recall list.

Pet food products are included in FDA's searchable database of recalled products. The database is located on the FDA Web site at *http://www.accessdata.fda.gov/scripts/peanutbutterrecall/index.cfm*. FDA has also established a consumer Web page that will keep consumers abreast of all updated information on the contamination and recall at *www.fda.gov/oc/opacom/hottopics/salmonellatyph.html*. The Web page has background on the investigation plus the testimony FDA officials presented to Congress.

Salmonella has been found in certain pet foods and pet treats containing peanut butter or peanut products, including dog and cat treats and bird food. People can get *Salmonella* infections from handling contaminated pet products, touching infected pets (i.e., contact with pet feces, the anus, or hair around the anus of the pet), or cleaning up after their infected pets. Dogs and cats might not show signs of salmonellosis, but can be carriers of *Salmonella* and infect other animals or humans.

Owners who believe their pets may have eaten any of the products on the FDA recall list and have concerns that the pets may have salmonellosis may want to bring their pets to a veterinarian.

Veterinarians can report complaints about pet food and other animal feed to the FDA by calling the FDA Consumer Complaint Coordinator in their States. Contact information can be found at *http://www.fda.gov/opacom/backgrounders/complain.html*. Reports should include product details, such as the lot number, brand name, expiration date, manufacturer or distributor, and purchase location. Reports should also include medical information that includes a veterinarian's report and diagnosis, signs of illness, numbers of animals who consumed suspected product and that do and do not have the signs, and complete medical histories of the animals. Additionally, veterinarians should consider contacting the manufacturer so any necessary investigation can be initiated immediately.

Consumers may also wish to report the illness to the product manufacturer. The contact information should be available on the product package or the company's Web site.

CDC is recommending to veterinarians that they talk to their clients about what precautions to follow in order to minimize the risk of illness to their families and how to safely clean up after their pets. It is also important to provide treatment recommendations and provide contact information if they have any additional questions.

Vitamin K Substances and Animal Feed

Editor's Note: *Although vitamin K is an important nutrient for animals and several sources are available, not all of those sources can or should be used in animal feed. Many have not been approved for use in the United States. Here's an overview of appropriate use of vitamin K ingredients in the United States.*

by Padmakumar B. Pillai, B.V.Sc.&A.H., M.V.Sc., Ph.D., Biologist, Division of Animal Feeds; Michaela G. Alewynse, Ph.D., Leader, Nutrition and Labeling Team, Division of Animal Feeds; and Sharon A. Benz , Ph.D., Director, Division of Animal Feeds, Center for Veterinary Medicine's Office of Surveillance and Compliance

In his experiments to determine whether cholesterol was a dietary essential, Henrik Dam discovered a new substance, which he named vitamin K. In 1929, he observed a hemorrhagic syndrome in chicks fed a diet from which the sterols were extracted. Eventually, an active, anti-hemorrhagic factor was isolated from alfalfa and was identified as a vitamin K substance. The characterization of this anti-hemorrhagic factor was done by Edward Doisy of St. Louis University. Dam and Doisy shared the Nobel Prize in 1943 for the discovery of vitamin K and its chemical nature.

Green leafy vegetables are good source of vitamin K. Vitamin K is also found in liver, meat, milk, and egg yolk. The major clinical sign of vitamin K deficiency noticed in all species is the impairment of blood coagulation. Clinical signs include, but are not limited to, increased clotting time and hemorrhage. Acute cases of vitamin K deficiency might cause subcutaneous and internal hemorrhages. Vitamin K deficiency can also

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FDA Approves First... *(Continued)*

their development of the GE animals to determine how best to develop the data and information needed for the Center for Veterinary Medicine to review in applications, as well as to clarify sponsor responsibilities for the shipping and labeling of investigational GE animals carrying rDNA constructs, animal disposition, record keeping, and other considerations in the regulatory approval process.

For GE animals producing substances to be used in or as drugs, biologics, or devices for use in humans, the appropriate Center within FDA reviews the human health product. In all cases, CVM reviews the rDNA constructs in GE animals.

FDA's Center for Biologics Evaluation and Research (CBER) approved the human biologic based on the product's safety and efficacy. During the approval process, CVM reviewed the recombinant DNA construct in the goats that produces ATryn to determine the safety of the construct to the animals and its stability in the genome of the goats over seven generations. CVM found no adverse outcomes.

Also, CVM reviewed and concurred with the sponsor's plan to continue to monitor the construct and its expression for the lifetime of the approved product.

The Agency held an advisory committee meeting in January to seek the opinion about the biologic from outside experts, who agreed that ATryn is safe and effective. CVM also briefed the committee about the animal drug components of the application.

CVM Posts NARMS Executive Report on Web Site

The Center for Veterinary Medicine has posted on its Web site the National Antimicrobial Resistance Monitoring System-Enteric Bacteria (NARMS) Executive Report, summarizing and integrating data from sampling done in calendar year 2005.

The NARMS program is operated collaboratively by: CVM, which operates the retail meat sampling program; the U.S. Department of Agriculture, which gathers samples from animals; and the Centers for Disease Control and Prevention, which collects isolates from humans. All three issue their own reports on the data they collect under the program. CVM issued a report on the retail meat sampling program in October 2008.

The Executive Report, posted in February, combines data from all three parts of the NARMS program into one integrated report. In addition, this report allows for easy tracking of trends over all three arms of the NARMS program—human, animal, and retail meats.

The report summarizes *Salmonella* and *Campylobacter* isolates recovered in 2005 from food animals at Federally inspected animal slaughter plants, retail meats, and humans. Also, the report includes data from previous years.

The data are posted so that others can use the information for various scientific purposes. In fact, a key part of the NARMS program is research, and all three NARMS partners have used the data for that purpose, according to Dr. Patrick McDermott, the NARMS Director for CVM. All three partners "have been very productive" in their research activity, he added.

20 Years of Generic Veterinary Drugs: Serving Animals and the Public Health

In 1988, Congress passed the Generic Animal Drug and Patent Term Restoration Act (GADPTRA), giving the Food and Drug Administration the authority to approve generic animal drugs. Since then, the number of approved generic animal drugs has steadily increased. In fact, over the past 5 years, the Center for Veterinary Medicine has approved more generic new animal drug applications than new, or "pioneer," animal drugs.

A generic new animal drug is a copy of an approved pioneer animal drug that FDA has already determined to be safe and effective for its intended use or uses. The intent of Congress in passing GADPTRA was to create a program that allows generic animal drug sponsors the opportunity to bring their products to market without duplicating the scientific investigations required for establishing the safe and effective use of the pioneer animal drugs. In lieu of establishing new safety and effectiveness information, the generic drug sponsor must demonstrate that its generic product is bioequivalent to a reference pioneer drug as determined by FDA.

The program has worked well. Ken Harshman, D.V.M., leader of CVM's Generic Animal Drugs Team, says that the introduction of generic animal drugs to the marketplace has resulted in a reduction in the cost of animal drugs used in companion and food-producing animals. This reduction in cost benefits animal health by ensuring an adequate supply of affordable drugs for the prevention, treatment, and control of disease. In addition, the competitive environment resulting from the availability of generic animal drugs also serves as a stimulus for the pharmaceutical industry to develop new innovative drugs.

Since GADPTRA, CVM has approved more than 270 original generic animal drug applications. The rate of approvals has been increasing. Ninety-four of these approvals, or 35 percent, were approved in just the past 5 years. (Also during the past 5 years, CVM approved 75 pioneer new animal drugs.)

Dr. Harshman attributes this increase in generic animal drug approvals to a growing interest among drug sponsors in the animal health industry to develop an inventory of generic animal drugs. As people see human generic drugs prescribed more frequently, animal owners inquire about the availability of less expensive generic drugs for their animals. This public awareness places a greater demand for the availability of more affordable generic animal drugs.

Dr. Ken Harshman, leader of CVM's Generic Animal Drugs Team

CVM's Generic Drug Team

CVM's Generic Animal Drugs Team is a part of the Center's Office of New Animal Drug Evaluation. The Generic Animal Drugs Team is responsible for addressing all requests for approval of generic new animal drugs.

GADPTRA allows a generic animal drug sponsor to submit an abbreviated new animal drug application (ANADA) to FDA to request approval of a generic copy of an off-patent pioneer new animal drug that FDA designates as a reference listed new animal drug. GADPTRA requires the generic sponsor to demonstrate that the generic animal drug is bioequivalent to the pioneer animal drug for the same approved indications and that the generic animal drug can be manufactured according to appropriate quality standards. The labeling for the generic new animal drug must also be the same as that approved for the reference new animal drug.

CVM allows sponsors to submit separate technical sections before submitting an ANADA for "phased review" instead of submitting all required information and data in a complete application. Under phased review, each technical section is reviewed independently with the intent of more efficiently completing the review process.

Completion of these technical sections is required for approval of a generic new animal drug:

- bioequivalence
- chemistry, manufacturing, and controls
- environmental
- labeling
- all other information

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20 Years of Generic Veterinary Drugs... *(Cont.)*

Phased review of each technical section is performed under a generic investigational new animal drug file. After all technical sections are completed, the sponsor then submits an Administrative ANADA to the Center requesting approval of the generic new animal drug. The time to completion of the Administrative ANADA is reduced, compared with a traditional ANADA, because no new data is reviewed during the assembly of the approval package documents.

Demonstrating bioequivalence

Pioneer drug sponsors must provide safety and effectiveness information, but generic drug sponsors must show that the generic new animal drug is "bioequivalent" to the pioneer, or reference, new animal drug.

Here are the three methods CVM accepts for determining bioequivalence, listed in order of preference.

- **Blood level study:** When absorption of the drug is sufficient to measure drug concentration directly in the blood and systemic absorption is relevant to the drug action, the generic drug sponsors should conduct a blood level bioequivalence study. The blood level study, which measures the rate and extent of drug absorption, is generally considered the most sensitive measure of bioequivalence. This approach is applicable to injectable drugs and most oral dosage forms intended to deliver the active drug ingredient to the systemic circulation. The blood level study compares pharmacokinetic parameters for the generic and reference drugs derived from measuring the drug concentrations in the blood as a function of time. Therefore, a validated assay method for measuring the active ingredient in the blood is essential in order to conduct a blood level pharmacokinetic study. Since the blood level study is the preferred method for determining bioequivalence, the sponsor should provide justification for choosing an alternative—either a pharmacologic or clinical end-point study—instead of a blood level study.
- **Pharmacologic end-point study:** A sponsor can use a pharmacologic end-point study when the measurement of drug concentration in the blood cannot be achieved or absorption in the blood is unrelated to drug action. This type of study requires that a pharmacological effect caused by the drug can accurately be measured and is relevant to drug action. Such effects may be things such as a change in gastric pH, metabolic by-products, or systemic blood pressure.
- **Clinical end-point study:** If drug concentrations in blood are not measurable or not relevant to drug action and there are no appropriate pharmacologic effects that can be monitored, then the generic drug sponsor can use a clinical end-point study to demonstrate bioequivalence. This method requires a comparison of the clinical effect of the generic product to the pioneer product and a comparison of each group to a placebo (or negative) control to ensure an adequate clinical challenge. Clinical endpoint studies have been used to support approval of some anthelmintics.

For each of the three methods, FDA has established the essential parameters that should be measured and the statistical methods that are employed to determine whether the criteria set for establishing the bioequivalence of the generic and reference new animal drugs are met.

Residues

The Center has determined that the tissue residue depletion of the generic animal drug is not adequately addressed through bioequivalence studies. Therefore, sponsors of generic drugs for food-producing animals will generally be asked to provide both bioequivalence and tissue residue studies for FDA evaluation. The generic animal drug will be assigned the withdrawal time supported by the residue depletion data. A shorter withdrawal period than that assigned the pioneer drug will be approved if the residue data are adequate and if no other human food safety concerns for the drug are evident.

Bioequivalence waiver

In some instances, a generic drug sponsor may be granted a waiver from the requirement to conduct a bioequivalence study for certain generic animal products. Categories of products that may be eligible for waivers include, but are not limited to, the following:

1. Parenteral solutions intended for injection
2. Oral solutions or other solubilized forms
3. Topically applied solutions
4. Inhalant volatile anesthetic solutions

In general, the generic product being considered for a waiver contains the same active and inactive ingredients in the same dosage form and concentration and has the same pH and physicochemical characteristics as an approved pioneer product. However, the Center will consider bioequivalence waiver requests for non-food animal topical products with

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20 Years of Generic Veterinary Drugs... *(Cont.)*

certain differences in the inactive ingredients of the pioneer and generic products.

If a waiver of the bioequivalence requirement is granted for a food-animal drug product, then the tissue residue depletion study is not required and the withdrawal period established for the pioneer product will be assigned to the generic product.

When generic and pioneer animal drugs differ

Not all generic applications are for exact copies of the pioneer animal drugs because GADPTRA permits changes to the generic animal product within certain defined limits. Consequently, a sponsor may submit an ANADA for a generic animal drug that is not identical to a pioneer animal drug in route of administration, dosage form, and strength, or in one active ingredient is substituted for one of the active ingredients in a combination new animal drug.

One other allowable change is the substitution of one Type A medicated article in a combination medicated feed.

To obtain permission from FDA to submit an application for an approval that is different than the pioneer, the sponsor must first be granted approval of a suitability petition requesting one or more of these allowable changes. These suitability petition requests generally are granted, unless investigations are required to demonstrate the safety and effectiveness of the generic animal drug.

If a suitability petition is granted, CVM requires that appropriate changes be made to the generic product labeling to ensure its safe and effective use. The labeled indications remain the same as the pioneer product even if one or more of these allowable changes is made to the generic product.

Emerging issues

Emerging issues involving generic drugs continue to present challenges for the Center. The determination of bioequivalence in domestic animal species can present a host of statistical and regulatory challenges such as sparse sampling of blood from small animals like cats, poultry, or fish. Generating a pharmacokinetic profile of a drug can be difficult with just a few data points, but efforts are being made to explore alternative approaches to address such issues.

CVM is giving special consideration to products that are not systemically absorbed, such as topical skin products or mastitis preparations that are locally administered. The Center is also evaluating biomass products used in feed-base delivery systems in food-producing animals. New innovative

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AGDUFA to Bolster Generic Drug Review at CVM

On August 14, 2008, President Bush signed into law the Animal Generic Drug User Fee Act of 2008 (AGDUFA), the first user-fee program (animal or human) for generic drugs.

Under AGDUFA, the generic animal drug industry pays user fees that will provide essential resources to improve generic animal drug review times for the purpose of meeting established performance goals. This improvement allows companies to bring their approved generic animal drug products to the consumer in a greatly reduced time frame. These user fees will supplement resources appropriated by Congress for generic animal drug review.

FDA also has in place a user fee program for pioneer animal drugs. This program has been widely considered a success. In fact, AGDUFA was sent to Congress along with the proposal to reauthorize the user fee program for pioneer drugs—the Animal Drug User Fee Act (ADUFA). Congress also approved the re-authorization of the user fee program under ADUFA II.

It is anticipated that AGDUFA will generate an estimated $27 million in user fees over the next 5 years with FDA collecting $4.8 million in fiscal year 2009. (AGDUFA will be in effect during Fiscal Years 2009 – 2013.)

FDA has established time frames for reviewing original ANADAs, manufacturing supplemental ANADAs, administrative ANADAs, generic investigational new animal drug data submissions and protocols. The review time frames for these types of submissions will shorten over the next 5 years.

Over the years, Dr. Harshman has seen CVM's Generic Animal Drugs Team increase its level of performance. To the team's credit, this increase in number of approvals (especially in the past 5 years) has occurred in the face of a mounting workload. With the implementation of AGDUFA, the increase in resources will erase the backlog of applications and reduce the time to approval for a wide variety of generic products.

Vitamin K Substances and Animal Feed *(Cont. from page 4)*

lead to impaired bone mineralization due to inadequate levels of osteocalcin, a protein involved in bone mineralization.

Deficiencies may result from inadequate vitamin K in the diet, disruption of microbial synthesis within the gut, inadequate absorption from the intestine, ingestion of vitamin K antagonists (substances that counteract the effect of vitamin K), or the inability of the liver to utilize available vitamin K.

Vitamin K can exist in three forms, two of them are naturally occurring and one is a synthetic analogue.

- Vitamin K1, also known as phytonadione or phylloquinone, is the form of vitamin K that occurs naturally in plants.
- Vitamin K2, or menaquinone, also naturally occurring, is the fat soluble

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20 Years of Generic Veterinary Drugs . . . *(Cont.)*

therapeutic approaches, such as transdermal or transbuccal delivery systems, present further challenges in developing new ways to evaluate product bioequivalence.

Therefore, as science moves forward and bioequivalence concepts are applied to support the approval of formulation changes or new drug delivery systems, regulators, innovator firms, and generic drug sponsors will face new challenges. These ongoing challenges provide the Generic Animal Drugs Team the opportunity to work with industry and other international regulatory agencies to develop new approaches and study models that may potentially provide solutions to these and other emerging bioequivalence issues.

CVM's Generic Drugs Team Headed by Dr. Ken Harshman

The Generic Drugs Team at the Center for Veterinary Medicine is led by Dr. Ken Harshman, a veterinarian with more than 20 years practice experience and a background in pharmacology.

Dr. Harshman became the Generics Drugs Team leader in June 2006. He first came to CVM in November 2002, joining the Generic Drugs Team.

Before that, he was a practicing veterinarian, with two clinics in northern Montana. One of the clinics focused on small animals. The other was a mixed animal practice, and his patients included cattle, horses, and an occasional American bison. (He said treating bison posed some special problems. For as large as the animals are, they can be very quick, he said.)

Dr. Harshman received his D.V.M. from Colorado State University College of Veterinary Medicine, and his Master's degree in pharmacology from the University of Utah.

His staff currently numbers 12, an increase of four since Congress passed the Animal Generic Drug User Fee Act (AGDUFA). As additional resources become available under AGDUFA, the team will be expanded to total 16.

Conclusion

Congress had lower drug development costs in mind when it passed GADPTRA in 1988. By avoiding the time and expense of developing and conducting safety and effectiveness studies, generic manufacturers can bring generic equivalent drugs to market at a lower cost. Animal owners and caretakers benefit from less expensive generic drugs for their animals.

FDA believes that generic drugs help decrease the cost of animal drugs and increase the variety of products available, just as it has with human drugs. This reduction in costs benefits everyone interested in animal health by ensuring an adequate supply of affordable drugs for the prevention, treatment and control of disease.

At the same time, generic competition in the marketplace stimulates pioneer drug companies to develop more innovative drugs. As a consequence, all aspects of the animal health industry benefit because a greater diversity and ample supply of therapeutic products are made available to protect the health of animals and people.

No one can tell how many new pioneer drugs have been developed because of the increased competition from generic animal drugs. But GADPTRA has worked. And now with the Animal Generic Drug User Fee Act signed into law (see sidebar, "Animal Generic Drug User Fee Act (AGDUFA) to Bolster Generic Drug Review at CVM,") the Center will now have additional resources to meet the challenges of regulating the approval of safe and effective generic new animal drugs.

Vitamin K Substances and Animal Feed *(Continued)*

form of vitamin K synthesized by the bacteria in the intestinal tract. Bacteria synthesize a range of related forms of this vitamin. These vitamin K analogues are collectively known as K2.

- Vitamin K3, also known as menadione, is the synthetic, water soluble analogue of vitamin K that can be converted to K2 in the intestine. Enzymes in mammalian and avian tissues are also capable of converting menadione to the active forms of vitamin K.

Ever since its initial discovery, vitamin K has been known to be important in the clotting process of blood, because of its involvement in the synthesis of four plasma clotting proteins. These proteins are factor II (prothrombin) and factors VII, IX, and X. More recent studies have shown that vitamin K also plays a role in calcium metabolism. According to the National Research Council's (NRC's) publication, Vitamin Tolerances of Animals (1987), the dietary adequacy of vitamin K is often defined as the amount of the vitamin needed to maintain normal levels of plasma vitamin-K-dependent clotting factors.

Poultry, such as broiler chickens and turkeys, are more likely to develop signs of vitamin K deficiency than other species of animals, which can be attributed to their short digestive tract and the fast rate of food passage. Ruminant animals such as cattle and sheep do not appear to need a dietary source of vitamin K due to the microbial synthesis of this vitamin that occurs in rumen, one of the compartments of the stomach of these animals. Since horses are herbivores, their vitamin K requirements may be met from sources present in plants and from microbial synthesis in the lower gut.

Different sources of vitamin K, including those that are listed in the Association of American Feed Control Officials' Official Publication as accepted for use in animal feed, are broadly denoted as vitamin K active substances. There are two vitamin K active substances that are prior sanctioned for use in poultry feed. (Prior sanction means that these vitamin K active substances were used in poultry feeds prior to 1958, so they have a history of safe use, and they are the subject of a formal FDA sanction of the ingredient for a particular use; the sanction is generally in the form of a letter from FDA stating that the use is acceptable.) These prior sanctioned substances are menadione and menadione sodium bisulfite complex. These two compounds are also widely used in other types of animal feeds, including pet foods, as animal nutritionists often formulate diets with vitamin K active substances in order to prevent vitamin K deficiencies.

Menadione dimethylpyrimidinol bisulfite and menadione nicotinamide bisulfite are vitamin K active substances that are regulated as food additives for use in animal feed. Federal regulation 21 CFR 573.620 lays out how menadione dimethylpyrimidinol bisulfite must be used in feed. Menadione dimethylpyrimidinol bisulfite is a nutritional supplement for the prevention of vitamin K deficiency in chicken and turkey feeds at a level not to exceed 2 g per ton of complete feed, and in the feed of growing and finishing swine at a level not to exceed 10 g per ton of complete feed.

Menadione nicotinamide bisulfite is also used as a nutritional supplement for both the prevention of vitamin K deficiency and as a source of supplemental niacin in poultry and swine. Federal regulation 21 CFR 573.625 states that this substance can be added to chicken and turkey feeds at a level not to exceed 2 g per ton of complete feed, and to growing and finishing swine feeds at a level not to exceed 10 g per ton of complete feed.

Before either menadione dimethylpyrimidinol bisulfite or menadione nicotinamide bisulfite could be used in a manner different from that specified in the appropriate regulation, a new food additive petition would need to be submitted and approved by the Food and Drug Administration.

Substances with vitamin K activity are often added to animal diets to ensure that animals do not develop vitamin K deficiencies. Even though vegetable sources contain fairly high amounts of vitamin K, very little is known about the actual bioavailability of the vitamin from these sources. According to NRC's publication, Vitamin Tolerances of Animals (1987), based on the limited amount of available information, vitamin K did not result in toxicity when high amounts of phylloquinone, the natural form of vitamin K, are consumed. It is also noted that menadione, the synthetic vitamin K usually used in animal feed, can be added up to levels as high as 1,000 times the dietary requirement without seeing any adverse effects in animals, except in horses. Administration of these compounds by injection has produced adverse effects in horses, and it is not clear if these effects would also occur when vitamin K active substances are added to the diet. Vitamin K and the vitamin K active substances serve important roles in providing an essential nutrient in animal diets.

Conclusion

Vitamin K is an important nutrient for all animals, but not all sources are safe for the animal, and some may raise food safety concerns. Therefore, feed formulators and livestock producers should be aware of what sources of vitamin K are appropriate for the animals they are feeding and choose ingredients accordingly.

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Shearer, M. J. Vitamin K. Lancet. 1995. 345(8944):229-234 *http://lpi.oregonstate.edu/infocenter/vitamins/vitaminK/*

Regulatory Activities: Warning Letters December 2008 – March 2009

WARNING LETTER TO: Ronald A. Brann, owner, Brann Farms: Lynden, WA

Reason for Letter: Violative drug residues

Date: March 10, 2009

An analysis by the U.S. Department of Agriculture's Food Safety and Inspection Service (FSIS) of tissue from an animal sold on July 29, 2008, by the firm found penicillin in the kidney at 0.49 parts per million (ppm). FDA has established a tolerance of 0.05 ppm for residues of penicillin in the uncooked edible tissues of cattle. The presence of this drug in the kidney of this animal in an amount exceeding the established tolerance causes the food to be adulterated within the meaning of the Federal Food, Drug, and Cosmetic Act (FFDCA).

An FDA inspection also found that the firm held animals under conditions that are so inadequate that medicated animals bearing potentially harmful drug residues are likely to enter the food supply. The firm lacks an adequate system to ensure that animals medicated by the firm have been withheld from slaughter for appropriate periods of time to permit depletion of potentially hazardous residues of drugs from edible tissues. For example, the firm failed to maintain treatment records, and it lacks an adequate inventory system for determining the quantity of drugs used to medicate its animals, the Warning Letter said. Food from animals held under such conditions is adulterated within the meaning of the FFDCA.

WARNING LETTER TO: Mark V. Porter, owner; Mark V. Porter dba MVP Livestock, Inc.: Sunnyside, WA

Reason for Letter: Violative drug residues

Date: February 11, 2009

During a November 17-18, 2008, inspection of the firm's operation Grandview, WA, investigators confirmed that cattle sold by the farm contained residues in excess of established safe tolerances. An analysis of tissue from the Holstein dairy cows sold by the firm disclosed flunixin at a level of 1.35 ppm in the liver and 0.046 ppm in muscle from a cow sold in July 2007; penicillin at a level of 0.18 ppm in kidney tissue from a cow sold in January 2008; penicillin at 0.20 ppm in kidney tissue from a cow sold in March 2008; and sulfadimethoxine at 4.66 ppm in liver tissues from a cow sold in April 2008. FDA has established a tolerance of 0.05 ppm for negligible residues of penicillin in the uncooked edible tissues of cattle, a tolerance of 0.1 ppm for negligible residues of sulfadimethoxine in the uncooked edible tissues of cattle, and a tolerance of 0.125 ppm for residues of flunixin in the liver tissue of cattle.

The Warning Letter also said that the firm has animals held under conditions that are so inadequate that medicated animals bearing potentially harmful drug residues are likely to enter the food supply. The letter said that the firm failed to inquire about the medication status of the animals that it purchased and delivered for sale to a slaughter plant when it delivered the cattle on the dates mentioned. It also failed to maintain treatment records for the animals that had been medicated. Food from animals held under such conditions is adulterated within the meaning of the FFDCA.

WARNING LETTER TO: Jean M. Osen, D.V.M., president, Medford Veterinary Clinic: Medford, WI

Reason for Letter: Improper extralabel drug use

Date: February 5, 2009

During an investigation in October 2008, FDA found that the use by a veterinarian employed by the firm of the new animal drug sulfadimethoxine caused the drug to be unsafe and adulterated within the meaning of the FFDCA. For example, the investigation found that the veterinarian used a brand of sulfadimethoxine oral solution to treat a lactating dairy cow in an extralabel manner, but that use is prohibited by regulation. In addition, the firm used a bolus dosage form of sulfadimethoxine to treat mastitis in lactating dairy cattle, which is an extralabel use, also prohibited by regulation.

WARNING LETTER TO: Acker Farms, Inc., Randy J. Acker, owner: Waunakee, WI

Reason for Letter: Violative drug residues

Date: January 30, 2009

On or about March 3, 2008, Mr. Acker sold a dairy cow for slaughter that contained flunixin at 1.34 ppm in its liver tissue, and 0.351 ppm in its muscle tissue, according to an analysis by FSIS.

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Warning Letters *(Continued)*

Also, on or about July 25, 2008, a dairy cow consigned by Mr. Acker was slaughtered, and an FSIS analysis of the tissue from the animal found that it contained flunixin at 1.21 ppm in its liver tissue and 0.173 ppm in its muscle tissue. FDA has established a tolerance of 125 parts per billion (ppb) (or 0.125 ppm) in the liver tissue and 25 ppb (or 0.025 ppm) in muscle tissue of cattle. The presence of this drug in edible tissues from these animals in these amounts causes the food to be adulterated within the meaning of the FFDCA.

An FDA investigation found that the firm kept animals under inadequate conditions, failed to maintain complete treatment records so medicated animals bearing potentially harmful drug residues were likely to enter the food supply, and administered drugs extralabely to food producing animals rendering them adulterated.

FDA's investigation found that the firm administered flunixin meglumine to a dairy cow without following the route of administration as stated in the approved labeling. The extralabel use of flunixin meglumine was not under the supervision of a licensed veterinarian, which is a violation of the regulations covering extralabel drug use in animals. In addition, the firm's extralabel use of flunixin meglumine resulted in illegal drug residue. In addition, FDA's investigation found that the firm administered sulfadimethoxine to lactating dairy cows without following the route of administration and animal class as stated in the approved labeling, as well as mixing this drug with oxytetracycline. Sulfadimethoxine is prohibited for extralabel use in lactating dairy cattle by regulation. Mixing oxytetracycline with other drugs is not in accordance with its approved labeling.

Furthermore, FDA's investigation found that the firm administered neomycin sulfate to lactating dairy cows contrary to the route of administration and animal class set forth in the approved labeling, and did so without the supervision of a licensed veterinarian, in violation of applicable regulations.

Because the firm's use of these drugs was not in conformance with their approved labeling and did not comply with appropriate regulations, the firm caused the drugs to be unsafe and adulterated within the meaning of the FFDCA.

WARNING LETTER TO: Dennis L. Acker: Waunakee, WI

Reason for Letter: Violative drug residues

Date: January 30, 2008

On or about May 19, 2008, Mr. Acker consigned a lot of seven cows and one bull for sale to be slaughtered. On or about May 20, 2008, one of the cows was slaughtered and its liver tissue was found to contain 5.40 parts per million (ppm) sulfadimethoxine, according to an FSIS analysis of the tissue. FDA has established a tolerance of 0.1 ppm for residues of sulfadimethoxine in the uncooked edible tissue of cattle. The presences of this excess amount in uncooked edible tissue cause the food to be adulterated.

Also, the investigation found that the firm held animals under conditions that are so inadequate that medicated animals bearing potentially harmful drug residues may enter the food supply. Food from animals held under such conditions is adulterated within the meaning of the FFDCA. FDA said that Mr. Acker's operation lacks a system to ensure that animals it buys, holds, and then sells for slaughter as food have not been medicated or, if they have been medicated, that the animals are withheld from slaughter for an appropriate period of time to deplete potentially hazardous residues of drugs from edible tissues.

WARNING LETTER TO: Lodi Veterinary Hospital, Michael S. Etter, D.V.M., president; K.C. Brooks, D.V.M., vice president; Scott T. Pertzborn, D.V.M., secretary-treasurer: Lodi, WI

Reason for Letter: Improper extralabel drug use

Date: January 30, 2009

An investigation conducted by FDA on September 5 and 10, 2008, regarding the use of drugs at the Lodi Veterinary Hospital in Lodi, WI, revealed that veterinarians caused the new animal drug sulfadimethoxine to be unsafe because the drug was used in a manner that did not conform with its approved uses or with the regulations for extralabel drug use in animals.

The firm prescribed and sold sulfadimethoxine to be mixed with oxytetracycline for extralabel use in lactating dairy cows; the firm used sulfadimethoxine oral 12.5% solution, which is not approved for use in lactating dairy cows, and labeled it for intravenous injection after mixing with oxytetracycline. Extralabel use of any sulfonamide drugs in lactating dairy cows is prohibited.

WARNING LETTER TO: Dale and Peggy De Grave Farm, Dale A. De Grave, owner: Casco, WI

Reason for Letter: Violative drug residues

Date: January 29, 2009

An FSIS analysis of tissues from a dairy cow Mr. De Grave sold on or about March 11, 2008, slaughter showed

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Warning Letters *(Continued)*

that the liver tissue contained flunixin at 0.261 parts per ppm and the presence of sulfamethazine at 29.78 ppm. FDA has established a tolerance of 125 parts per billion (ppb) (or 0.125 ppm) of flunixin in the liver tissue. FDA has not established a tolerance for residues of sulfamethazine in the edible tissues of female dairy cattle 20 months of age or older. The presence of these drugs in edible tissues from this animal in these amounts causes the food to be adulterated.

FDA said in the Warning Letter that its investigation found that the firm kept animals under inadequate conditions, failed to maintain complete treatment records so medicated animals bearing potentially harmful drug residues were likely to enter the food supply, and administered sulfonamide drugs extralabely to food producing animals rendering them adulterated.

WARNING LETTER TO: D&D Hawkins Dairy, Inc., Douglas J. Hawkins, co-owner; Dennis Hawkins, co-owner: Chippewa Falls, WI

Reason for Letter: Violative drug residues

Date: January 27, 2009

On or about July 8, 2008, D&D Hawkins Dairy, Inc., sold a veal calf for slaughter as food, and an FSIS analysis found that the calf had desfuroylceftiofur (the marker residue for ceftiofur) at 6.24 ppm in its kidney tissue and the presence of flunixin at 3.17 ppm in its liver tissue. FDA has not established a tolerance for residues of desfuroylceftiofur or flunixin in the edible tissue of veal calves. The presence of these drugs in the edible tissue of this animal causes the food to be adulterated.

FDA said in the Warning Letter that its investigation found that the firm held animals under conditions that are so inadequate that medicated animals bearing potentially harmful drugs residues are likely to enter the food supply. For example, the firm fed discarded milk from cows treated with medications to calves that were intended for slaughter as food.

WARNING LETTER TO: Mr. Paul E. Endsley, president, Endsley Dairy Farm, LLC : Hastings, MI

Reason for Letter: Violative drug residues, improper extralabel drug use

Dated: January 5, 2009

An FSIS analysis of tissues from an animal sold by the firm on May 20, 2008, revealed the presence of gentamicin in the kidney. There is no allowable tolerance for gentamicin in cattle. The presence of gentamicin in this animal causes the food to be adulterated within the meaning of the FFDCA.

An FDA investigation also found that the firm held animals under conditions that are so inadequate that medicated animals bearing potentially harmful drug residues are likely to enter the food supply. For example, the firm failed to maintain complete treatment records. Food from animals held under such conditions is adulterated within the meaning of the FFDCA.

FDA's investigation also found that the firm administered gentamicin to a dairy cow without following the animal class as stated in the approved labeling. That extralabel use of gentamicin was not under the supervision of a licensed veterinarian, which is a violation of the regulations covering extralabel drug use in animals and resulted in an illegal drug residue. Because the use of this drug was not in conformance with its approved labeling and did not comply with the applicable regulations, the firm caused the drug to be unsafe and adulterated under the FFDCA.

WARNING LETTER TO: Kidron Auction, Inc., John E. Sprunger, president: Kidron, OH

Reason for Letter: Violative drug residues

Date: December 30, 2008

The firm offered an animal for sale for slaughter as food that was adulterated. On or about February 14, 2008, a calf was consigned for sale at Kidron Auction, Inc., and this calf was later found to be adulterated. An FSIS analysis of the kidney tissue from the animal found that the tissue contained 99.30 ppm of neomycin. FDA has established a tolerance of 7.2 ppm has been established for residues of neomycin in the kidney tissue of cattle. This illegal residue was caused by using a soluble powder containing neomycin sulfate that is not approved for use in veal calves.

Also found in the tissue analysis of this animal were 0.22 ppm sulfamethoxazole and 0.075 ppm flunixin in the liver, and 0.27 ppm sulfamethoxazole and 0.021 ppm flunixin in the muscle. FDA has not established a tolerance for sulfamethoxazole or flunixin residues in edible tissues of veal calves. The presence of these drugs renders the animal adulterated.

FDA's investigation of Kidron Auction, Inc. found that adulterated animals were sold at auction and that the animals were held under inadequate conditions, which resulted in medicated animals bearing potentially harmful drug residues entering the food supply. Specifically, the firm lacked a system to ensure that animals bought

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Warning Letters *(Continued)*

and sold for slaughter as food have not been medicated or, if they are medicated, they have been withheld from slaughter for an appropriate time to deplete the potentially hazardous residues of drugs from edible tissues.

WARNING LETTER TO: Todd Troyer: London, OH

Reason for Letter: Violative drug residues

Date: December 22, 2008

An FSIS analysis of tissue samples from a veal calf sold by Todd Troyer on or about February 14, 2008, found 99.30 ppm of neomycin in the kidney tissue. FDA has established a tolerance of 7.2 ppm for residues of neomycin in the kidney tissue of cattle. This illegal residue was caused by using a soluble powder containing neomycin sulfate that is not approved for use in veal calves.

In addition, the FSIS analysis of tissue samples collected from this animal identified the presence of 0.22 ppm sulfamethoxazole and 0.075 ppm flunixin in the liver and 0.27 ppm sulfamethoxazole and 0.021 ppm flunixin in the muscle of this animal. FDA has not established a tolerance for sulfamethoxazole of flunixin residues in the edible tissue of veal calves, and the presence of these drugs renders the animal adulterated.

The Warning Letter said that Mr. Troyer had sold an adulterated veal calf for slaughter, held animals under conditions that were so inadequate that medicated animals bearing potentially harmful drug residues were likely to enter the food supply, adulterated the new animal drugs neomycin, sulfamethoxazole and flunixin through extralabel use.

WARNING LETTER TO: Douglas Bennett Farm; Mr. Douglas Bennett, co-owner: Johnson, VT

Reason for Letter: Violative drug residues

Date: December 5, 2008

An FSIS analysis of tissues from an adult dairy cow that the firm sold on or about February 18, 2008, for slaughter as food found 0.66 ppm of sulfamethazine in the liver and 32.91 ppm in the muscle. The analysis also found detectable levels of gentamicin in the kidney. FDA has not established a tolerance for sulfamethazine in the uncooked edible tissue of adult dairy cows or a tolerance for gentamicin in the uncooked edible tissues of cattle. The presence of these drugs in the edible tissue of the animal caused the food to be adulterated.

The investigation found that the firm held animals under conditions that were so inadequate that medicated animals bearing potentially harmful drug residues were likely to enter the food supply, and it adulterated the new animal drug sulfamethazine through extralabel use.

WARNING LETTER TO: Erik Martinez, president and chief executive officer, Virbac, Inc.: Fort Worth, TX

Reason for letter: Violations of current Good Manufacturing Practices

Date: December 10, 2008

During an inspection of the firm facilities in Bridgeton, MO, in July 2008, FDA investigators found violations of current Good Manufacturing Practices. The documented violations cause the products to be adulterated under the FFDCA.

In addition, the Warning Letter said that the company had issued promotional material making claims that products were more effective than had been demonstrated by substantial evidence or substantial clinical experience. Therefore, FDA considers the products to be misbranded.

WARNING LETTER TO: Carol A. Weyandt, owner, B & C Calves/Livestock: Claysburg, PA

Reason for Letter: Violative drug residues

Date: November 26, 2008

An FSIS analysis of tissues collected from a bob veal calf sold by the firm on or about January 25, 2008, found 15.07 ppm neomycin in the kidney tissue. FDA has not established a tolerance for residues of neomycin in kidney tissue from veal calves, so food from the animal would be considered adulterated under the FFDCA.

WARNING LETTER TO: Jose L. Gonzalez, co-owner, Gonzalez Dairy, LLC: Mesquite, NM

Reason for Letter: Violative drug residues, improper extralabel drug use

Date: November 24, 2008

An FSIS analysis of tissue from a Holstein cow sold by the firm on or about July 3, 2008, and slaughtered for food was found to have 10.19 ppm of sulfamethazine in the liver. FDA has established a tolerance of 0.1 ppm for residues of sulfamethazine in the edible tissues of cattle. The presence of the drug in edible tissues causes the

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Warning Letters *(Continued)*

animal to be considered adulterated under the FFDCA. The investigation also found that the firm held animals under conditions that were so inadequate that medicated animals bearing potentially harmful drug residues were likely to enter the food supply.

In addition, FDA's investigation found that the firm administered sulfamethazine to a Holstein cow without following the dose and withdrawal times as stated in the approved labeling. Specifically, the firm administered three 32.1-g boluses of a sulfamethazine product per day for 3 consecutive days although the drug label indicated that a 1,000-lb. cow should receive no more than five boluses within a 72-hour period. Also, the label states, "WARNING: Animals intended for human consumption should not be slaughtered for food for at least 12 days after the last dose. Exceeding two consecutive doses may cause violative tissue residues to remain beyond the withdrawal time." The firm's extralabel use of sulfamethazine was not under the supervision of a licensed veterinarian, in violation of regulations, and the firm's extralabel use of sulfamethazine resulted in an illegal drug residue. Because the firm's use of this drug was not in conformance with its approved labeling and did not comply with applicable regulations, the firm caused the drug to be unsafe and adulterated under the FFDCA.

WARNING LETTER TO: John M. Mellott, owner, John Mellott Farm: Mercersburg, PA

Reason for Letter: Violative drug residues

Dated: November 12, 2008

An FSIS analysis of tissue from an animal sold on or about February 14, 2008, for food by the firm was found to contain 8.42 ppm neomycin in the kidney. FDA has established a tolerance 7.2 ppm for residues of neomycin in the kidney of cattle. The presence of neomycin in this amount in the kidney from the animal causes the food to be adulterated under the FFDCA.

An FDA investigation also found that the firm held animals under conditions so inadequate that medicated animals bearing potentially harmful drug residues are likely to enter the food supply. For example, the Warning Letter said that the firm failed to maintain treatment records. Food from animals held under such conditions is adulterated under the FFDCA.

WARNING LETTER TO: Richard E. States: Hesston, PA

Reason for Letter: Violative drug residues

Dated: October 24, 2008

An FSIS analysis of tissue from a bob veal calf sold by Mr. States' operation on or about April 9, 2008, found flunixin at 0.149 ppm in the liver. FDA has not established a tolerance for residues of flunixin in the edible tissues of veal calves. The presence of flunixin in edible tissues from this animal in this amount causes the food to be adulterated under the FFDCA.

The investigation also found that the firm held animals under conditions so inadequate that medicated animals bearing potentially harmful drug residues were likely to enter the food supply. For example, the firm failed to maintain complete treatment records. Food from animals held under such conditions is adulterated under the FFDCA.

Approvals for November 2008–March 2009

CVM has published in the *Federal Register* notice of the approval of this New Animal Drug Applications (NADA)

TOPMAX 9 (ractopamine hydrochloride) Type A medicated article (NADA 141-290), filed by Elanco Animal Health, A Division of Eli Lilly & Co., Indianapolis, IN. The Type A medicated article is used to make Type B and Type C medicated feeds used for

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Approvals for November 2008 – March 2009 *(Continued)*

increased rate of weight gain and improved feed efficiency in finishing turkeys. Notice of approval was published December 1, 2008.

CVM has published in the *Federal Register* notice of the approval of these Supplemental New Animal Drug Applications (NADA)

OPTAFLEXX (ractopamine hydrochloride), HEIFERMAX 500 (melengestrol acetate), and RUMENSIN (monensin), and TYLAN (tylosin phosphate) Type A medicated articles (supplement to ANADA 200-424), filed by Ivy Laboratories, Division of Ivy Animal Health, Inc., Overland Park, KS. The supplemental NADA provides for an increased level of monensin in four-way combination Type C medicated feeds containing ractopamine, melengestrol, monensin, and tylosin for heifers fed in confinement for slaughter; and a revision to bacterial pathogen nomenclature. Notice of the approval was published December 11, 2008.

TYLAN (tylosin phosphate) Type A medicated article (supplement to NADA 012 491), filed Elanco Animal Health, A Division of Eli Lilly & Co., Indianapolis, IN. The supplement provides for use of tylosin tartrate in medicated drinking water for swine for 3 to 10 days followed by administration of tylosin phosphate in medicated swine feed for 2 to 6 weeks for the control of porcine proliferative enteropathies (PPE, ileitis) associated with *Lawsonia intracellularis*. Notice of the approval was published December 18, 2008.

TYLAN (tylosin tartrate) Soluble (supplement to NADA 013 076), filed by Elanco Animal Health, A Division of Eli Lilly & Co., Indianapolis, IN. The supplement provides for use of tylosin tartrate in medicated drinking water for swine for 3 to 10 days followed by administration of tylosin phosphate in medicated swine feed for 2 to 6 weeks for the treatment and control of swine dysentery associated with Brachyspira hyodysenteriae and for the control of porcine proliferative enteropathies (PPE, ileitis) associated with *Lawsonia intracellularis*. Notice of the approval was published December 18, 2008.

CVM has published in the *Federal Register* notice of the approval of this Abbreviated New Animal Drug Applications (NADA)

VETAZINE Cream (triamcinolone acetonide) (ANADA 200-459), filed by Modern Veterinary Therapeutics, LLC, Coral Gables, FL. The ANADA provides for veterinary prescription use of Cream on dogs for topical treatment of allergic dermatitis and summer eczema. Modern Veterinary Therapeutics, LLC's VETAZINE Cream is approved as a generic copy of VETALOG Cream, sponsored by Fort Dodge Animal Health, A Division of Wyeth Holdings Corp., under NADA 046-146. Notice of the approval was published December 29, 2008.

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